REMARKS

Claims 4, 6, 7, 9, 10, 12, 13, 78, and 80-83 are pending. Claims 1-3, 5, 8, 11, 14-77, 79 and 84-88 have been canceled. Applicants reserve the right to pursue the subject matter of the canceled claims in a subsequent application, related application. No new matter has been added and entry of the amendment is respectfully requested.

Interview

Applicants and their representative thank the Examiner and her Supervisor for the courtesy shown during the personal interview conducted on August 16, 2005. Specifically, the utility rejections and the prior art rejections were discussed and the interview summary agreed upon and placed on the record. Applicants and their representatives appreciate the time the Examiner and her Supervisor took to discuss the issues in the present case.

Supported by a Credible, Specific and Substantial Utility

Claims 4-7, 9-13, and 78-83 are variously rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a credible, specific, or substantial asserted utility or a well established utility. Applicants respectfully traverse this rejection.

The Invention is Useful to Treat Prostate Cancer

Applicants respectfully submit that the present specification has asserted a number of uses for the 108P5H8 protein. For the purposes of this discussion, the claimed subject matter is asserted as being useful as a prostate cancer marker which may be used as a target for therapeutic molecules, such as antibodies which bind to the target. Applicants reserve the right to assert alternative or additional utilities if necessary. The asserted utility is a credible, specific, and substantial, which fulfills the requirement under 35 U.S.C. § 101.

Credible Utility

"To violate [35 U.S.C.] 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, (Fed. Cir.

1992) (emphasis added). As discussed in the M.P.E.P. at section 2107.01, situations where an invention is completely inoperative are rare and examples where the rejection has been upheld on appeal are rarer still. The Office has alleged that the asserted utility is not credible but has not stated why one of ordinary skill in the art would believe that the invention was completely inoperative. As discussed more fully below, there are a number of anti-cancer antibody therapeutics available on the market. In view of these products, those of ordinary skill in the art recognize that the presently asserted utility is credible.

Specific Utility

"[A] specific utility is particular to the subject matter claimed and would not be applicable to a broad class of invention." *In re Fisher*, 2005 U.S. App. LEXIS 19259, 18 (*citing* MPEP §2107.01). Claims 1-3 are drawn to a composition comprising an isolated or recombinant protein of SEQ ID NO: 8873 or SEQ ID NO:8875. Applicants have asserted that this protein can be used as a target to detect cancerous prostate cells. The Office has admitted that this asserted utility is specific. Office Acton, item 5, page 3.

Substantial Utility

A substantial utility is one that defines a "real world" or a "practical" use. MPEP §2107.01. "'Practical utility' is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." *Nelson v. Bowler,* 626 F.2d 853, 856 (C.C.P.A. 1980) Any reasonable use asserted by an applicant that provides a public benefit "should be accepted as sufficient, at least with regard to defining a 'substantial' utility." MPEP §2107.01, *see also Nelson* at 856.

Applicants have asserted that the protein component of the claimed composition is useful *inter alia*, as a therapeutic target for the treatment of prostate cancer. Specification as published at paragraph [0027]. Figure 10 shows that that mRNA from the 108P5H8 gene was detected in a variety of cancers, such as prostate and pancreatic cancer. Figure 11 shows that various normal tissues, including normal prostate tissue, contain 108P5H8 mRNA. Figures 12-17 show detection of the 108P5H8 mRNA in a variety of sample types, including samples taken from patients.

Perhaps even more importantly, the data disclosed in Figure 21 and discussed in Example 8 of the specification indicate that Applicants have actually produced antibodies against the amino acid sequence of SEQ ID NO: 2570 that is expressed on the surface of prostate cancer cells. Figure 21 shows LNCaP and LAPC4 cells that were subjected to flow cytometric and fluorescence microscopic analysis of 108P5H8 expression using an anti-108P5H8 polyclonal antibody or control rabbit IgG. Fluorescence was monitored following incubation with an FITC-conjugated anti-rabbit IgG secondary antibody. The detected fluorescence on the surface of the target cells clearly indicates that the 108P5H8 protein is expressed on the surface of these cells. Based on the evidence discussed above, 108P5H8 proteins encoded by and translated from the mRNA detected in the target cells have substantial utility as prostate cancer markers.

In view of the data provided in the specification as well as the art-recognized need for additional prostate cancer markers, Applicants submit that the specification clearly asserts a substantial utility for the claimed invention.

Response to Cited References

The Office cited a number of references in support the present rejection. Applicants have reviewed these references and have concluded that none of the references support the Office's argument that one of ordinary skill in the art would reasonably believe that in cases where mRNA is detected that it is more likely than not that protein would not be present. Each of the cited papers is discussed below.

The first paper relied upon by the Office is Haynes et al., *Electrophoresis*, 19:1862-71 (1998). Applicants submit that a careful examination of the data and conclusions of Haynes et al., does not support the Office's assertion that the protein levels in a cell cannot be accurately predicted from the level of the corresponding mRNA transcript. First, applicants note that Haynes et al. is a review article, and such articles are typically not subject to rigorous peer review and do not necessarily present a complete picture of the data. In particular, the Haynes review lacks the rigorous statistical analysis of the correlation between mRNA and protein expression data needed to support its broad conclusions (See Figure 1). This statistical analysis was subsequently presented in

what appears to be the peer-reviewed version of very similar, if not identical data, in Gygi, et al., *Mol. Cell. Biol.* 19(3):1720-30 (1999). Applicants submit that the additional data in Gygi, et al. must be considered in weighing the broad conclusions asserted in the Haynes review and relied upon by the Office. After examining 106 genes with a strikingly similar expression profile to that first reported in the Haynes, Gygi et al. conclude that there was "a general trend of increased protein levels resulting from increased mRNA levels." *See* Gygi et al. at page 1726. In fact, the correlation coefficient for this general trend was 0.935. *See* Gygi et al., Figure 5. Thus, with a rigorous statistical analysis, the correlation between mRNA levels and protein expression was readily apparent.

Both the Haynes review and Gygi et al. indicate that the greatest variance in the correlation between mRNA level and protein expression occurs in the subset of mRNA transcripts present at 10 copies or less per cell. The detection limit of the Northern blot analysis employed in the instant specification make it difficult to detect routinely mRNA transcript present at 10 or less copies per cell.[1] Thus, it is questionable whether this subset of transcripts is even detectable in the Northern Blot analysis employed. Assuming *arguendo* that Northern Blot analysis permits the detection of such rare transcripts, both the Haynes review and Gygi et al. indicate that the protein expression resulting from this low mRNA copy subset is significantly below that of the protein expression from the high mRNA copy subset. For example, Figure 5 in Gygi et al. indicates that an mRNA transcript of ~45 copies/cell results in a protein abundance of ~50-100,000 copies/cell. On the other hand, an mRNA transcript of ~200 copies/cell results in a protein abundance of ~375,000 copies/cell. Such differences are not insubstantial and are readily detectable using well known and routine methods in the art. Therefore, while there is only an inexact correlation between mRNA and protein expression for the low mRNA copy subset, the range in protein expression resulting from this subset is still well below that observed within the high mRNA copy subset. Finally, neither the Haynes review nor Gygi et al. provides evidence or suggests that a high mRNA copy transcript does not result in high protein expression.

[1] Applicants note that the detection technology employed in the Haynes review and in Gygi et al. is the SAGE method. As indicated in Gygi et al., the SAGE method is a very sensitive mRNA detection method, permitting the detection of a single copy of mRNA per cell 72% of the time. *See* the Gygi et al., at page 1728, first column.

Futcher et al., *Mol. Cell. Biol.* 19(11): 7357-68 (1999), conducted a similar study to the one reported by Gygi et al., but reached markedly different conclusions. Futcher et al. observed a good correlation between mRNA and protein levels for 148 identified proteins in yeast. *See* Futcher et al., Figure 2.[2] These workers report a Spearman rank correlation, r_s, of 0.74 ($P < 0.0001$), and a Pearson correlation coefficient, r_p, on log transformed data of 0.76 ($P < 0.00001$). *See* Futcher et al., page 7360. Futcher et al. note that the statistical approach employed by Gygi et al. (Pearson correlation coefficient, r_p, on untransformed data) is parametric, and would only be valid if both mRNA and protein abundances were normally distributed, which was not the case. In contrast to the method employed by Gygi et al., Futcher et al. observed a good correlation even for samples at low protein abundance.

It is well known that tumor cells frequently show mixed histology and are therefore significantly more difficult to characterize than isolated cell lines. Applicants note that Chen et al., *Molecular and Cellular Proteomics*, 1: 304-313 (2002), which was also cited by the Office, compared protein and mRNA levels in frozen tissue samples taken from surgically resected lung adenocarcomas. *See* experimental section at page 306. Chen et al. reported that protein abundance correlated to corresponding mRNA levels in 17% (28 proteins) of the 165 protein spots examined. *See* Chen et al., Discussion at page 309 and Table II, page 311. While the overall correlation appears relatively low, Chen et al. note that the correlation is substantially higher than the amount predicted by chance (which was 5.1). *See* Chen et al., Discussion at page 312-13. Chen et al. suggest that this subset of proteins may represent a group of gene products that are regulated at the transcriptional level in these tissues. *See* Chen et al., Discussion at page 311). In contrast to the results in lung adenosarcoma, Orntoft et al., *Molecular & Cellular Proteomics*, 1: 37-45 (2002), disclose a highly significant correlation ($p < 0.005$) between protein levels and mRNA ratios for 19 of 26 (73.1%) well resolved, abundant proteins in bladder cancer. *See* Orntoft et al., page 42, Figure 4. Samples were obtained from fresh biopsy materials from invasive and benign bladder tumors. Protein levels (as judged by 2D-PAGE) showed a high correlation to the mRNA transcript ratio between matched samples of invasive and benign bladder tumors. *See* Orntoft et al., Discussion at

[2] Applicants note that Futcher et al. estimated mRNA abundance by SAGE and by hybridization of cRNA to oligonucleotide arrays; protein quantitation was determined by phosphorimaging of intact gels coupled to image analysis. *See* Futcher et al. at page 7360, left column.

page 44, right column, 2nd full paragraph. Given the heterogeneity of many tumors, applicants suggest that it is difficult to draw quantitative conclusions based on data from whole tumors.

The Office also cited Hu et al., *J. Proteome Research*, 2: 405-412 (2003), in support of the present rejection. Hu, et al. report an automated literature mining tool that attempts to estimate the relative strength of human gene-disease relationships. Applying this literature mining approach to a dataset of genes expressed in normal and cancerous breast tissue, Hu et al. discovered that genes with a 10-fold or more change in expression showed a strong correlation between expression level and published role in breast cancer for a subset of tumors, while those with a 5-fold or less change showed no correlation. *See* Hu et al. Discussion at page 412 and Table 3). Hu et al. note that the observed correlation was only found for estrogen receptor (ER) positive tumors, not for ER-negative tumors (possibly reflecting bias in the dataset), and emphasize that "caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *See* Hu et al., Discussion at page 412. Applicants respectfully submit that it is not possible to generalize from Hu et al. to determine a threshold correlation between gene over-expression and role in disease.

As discussed above, the conclusion that high mRNA expression correlates with high protein expression, which has been a central dogma of molecular biology, remains credible and is supported by a careful statistical analysis of studies in yeast cells. *See* foregoing discussion of Haynes et al.; Gygi et al.; and Futcher et al. While the results were less consistent in tumor samples, good correlation between mRNA and protein abundance was noted in bladder tumors (Orntoft et al.) and in a subset of lung andenosarcomas (Chen et al.). In view of the above discussion, the basis for this rejection may be withdrawn.

The Office also based the present rejection, in part, on the observation that the specification does not teach the functional role of the 108P5H8 polypeptide. The Federal Circuit has noted that "(i)t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests." *See Cross*, 753 F.2d at 1042, n.3, 224 USPQ at 749, n.3. Applicants respectfully submit that the practical utility of the 108P5H8 polypeptide as a cancer marker is not dependent upon the polypeptide's biochemical function, as the invention is not drawn to that subject matter. Nevertheless, it is noteworthy that a consistent biochemical characteristic of

prostate cancer is a marked decrease in zinc and citrate levels in malignant cells, suggesting that the loss in ability to accumulate zinc is an important factor in the development and progression of prostate cancer. *See, e.g.,* Costello, et al., *Prostate Cancer and Prostatic Diseases*, 7: 111-117 (2004). The observation that the 108P5H8 polypeptide, a zinc transporter protein, is associated with prostate cancer cells is suggestive that the protein may play a role in the pathogenesis of prostate malignancy.

As previously discussed, well-known prostate cancer markers, including PSMA, PSCA, and the widely used clinical marker, PSA, are expressed on both normal and cancerous prostate. The observation that 108P5H8 mRNA exhibits a similar expression profile to these recognized markers is unsurprising, and would not lead a skilled artisan to conclude that the 108P5H8 protein lacks utility as a diagnostic or therapeutic marker. In the context of immunotherapy, it is inconsequential that both normal and cancerous prostate cells express 108P5H8. First, on the basis of the differential mRNA expression data shown in the Specification at Figure 13, cancerous cells would be expected to produce larger amounts of the 108P5H8 polypeptide and to be targeted selectively by antibodies. Second, that those of skill in the art consider such markers to be acceptable targets for immunotherapy is evidenced by the clinical and preclinical efforts to develop antibody therapeutics for known prostate cancer markers. For example, clinical trials of two antibody therapeutics targeting PSMA are on-going.[3] Finally, because the established treatments for prostate cancer, including radiation therapy, chemotherapy and prostatectomy (surgical removal of part or all of the prostate gland) are not sparing of normal prostate tissue, the potential lack of specificity in targeting cancerous cells using antibody therapeutics is acceptable in this context.

Declaration

In addition to the data disclosed Example 8 of the specification which indicates that the amino acid sequence of SEQ ID NO: 2570 that is expressed on the surface of prostate cancer cells, Applicants offer the declaration of Dr. Karen Jane Meyrick Morrison under Rule 1.132. This

[3] J591, an yttrium-90 labeled anti-PSMA monoclonal antibody is reportedly in Phase II clinical trials for androgen-independent prostate cancer. MLN2704, an anti-PSMA monoclonal antibody conjugated to a chemotherapeutic drug, maytansinoid, is reportedly in Phase I/II clinical trials for metastatic androgen independent prostate cancer.

declaration shows immunohistochemistry data where prostate tumor samples were tested with a polyclonal antibody which binds to SEQ ID NO: 2570. The staining of the tumor sample clearly shows that the test antibody binds to the target antigen. This data clearly demonstrates that the protein recited in the claims can be detected, and thus targeted by therapeutic compositions, such as antibodies, as a treatment for prostate cancer.

The fact that certain normal tissues as well as cancerous prostate cells express the protein recited in the claims does not undermine the utility of the invention. A number of therapeutic antibodies which cross react with other are on the market, such as Herceptin® and Erbitux®, applicants submit that one of ordinary skill in the relevant art would find that the claimed subject matter is useful to target prostate cancer cells. Applicants submit with this response the Declaration of Dr. Steven B. Kanner concerning normal tissue expression and monoclonal antibodies that are being successfully used in the market for the treatment of cancer. Antibody vectors like the ones presently claimed can be labeled with toxins, radioisotopes or other chemotherapeutic agents to inhibit the growth of prostate cancer cells expressing the amino acid sequence of SEQ ID NO: 2570. As such, the present rejection has been overcome and should be withdrawn.

Written Description

Claims 11 and 78-83 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 11 and 79 have been canceled. These amendments obviate the reasons for the present rejection.

Anticipation

Claim 4 was rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Murgia, *et al.* As a preliminary matter, Applicants note that Murgia, *et al.* does not teach the sequence recited in the pending claims. Accordingly, as a matter of law, the polyclonal antibodies disclosed in that paper do not anticipate the subject matter of the pending claims. Nevertheless, solely to advance the prosecution of the present case, Applicants have amended claim 4 to recite monoclonal antibodies. Murgia, *et al.* do not teach or suggest monoclonal antibodies. Nor is there motivation in the

reference for the preparation of such antibodies. Accordingly, the reasons for the present rejection have been overcome and the rejection should be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 511582002500. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 27, 2005

Respectfully submitted,

By _____

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